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# FAILURE TO ACQUIRE AN INHIBITORY TASK FOLLOWING SEIZURE-INDUCED BRAIN DAMAGE[1]

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*Summary.*—Male rats that had displayed limbic seizures following a single pair of systemic injections of lithium and pilocarpine were trained 2 months later on an operant schedule that required differential low rates of responding (DRL). The seizured rats never acquired schedules that required either 6-sec. or 12-sec. inhibition of responses following a reward; these rats displayed more perseverative responding and shorter interresponse times than controls. Histomorphology indicated severe brain damage primarily within the entorhinal cortices (and adjacent amygdala) and dorsal thalamus.

Impulsivity and behavioral changes are expected sequelae of limbic seizure-induced brain damage. Honchar, Olney, and Sherman (1983) found that subcutaneous injections of lithium chloride (3 mequiv/kg), followed 24 hr. later by the muscarinic agent pilocarpine (30 mg/kg), produced limbic motor seizures within 30 min. and substantial alteration in membrane chemistry within 24 hr. Persinger, Makarec, and Bradley (1988) observed that insidious brain damage continued to evolve for weeks after the single injections, even though the animals had presumably recuperated. This study was designed to ascertain the severity of the behavioral effects due to this form of brain damage. The DRL (differential reinforcement of low rates of responding) schedule was selected because it is sensitive to disruptions in the capacity to inhibit behavior.

Seven male albino Wistar rats, 250 days of age, served as subjects. Four of the rats had displayed the usual limbic seizures within 30 min. after the subcutaneous (s.c.) injection of 30 mg/kg of pilocarpine (24 hr. after 3 mequiv/kg of lithium, s.c.). To ensure survival, these rats had also been injected 1 hr. after seizure onset with 25 mg/kg of acepromazine. Control rats had received only lithium or pilocarpine. For the two months before the DRL training, each rat was housed singly; during this time occasional limbic seizures (stereotyped myoclonic displays of forepaws followed by generalized convulsions) were observed about once per week within the group that had received the lithium-pilocarpine combination. One week before training, all rats were reduced to 85% body weight and maintained at this level for the remainder of the study.

Following two days of 30 min. of continuous reinforcement the rats

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were maintained on a DRL-6-sec. schedule for 20 days; this was followed by a DRL-12-sec. schedule for another 20 days. Interresponse-times (IRTs) within 1-sec. bins between 0—0.9, 1.0—1.9 . . . and 20 sec. or greater (truncated) were obtained using a microcomputer. To facilitate analyses, percentage of total IRT displayed within the 0—2 sec. and 5—7 sec. bins were compared for each group for the first three and last three days of training.

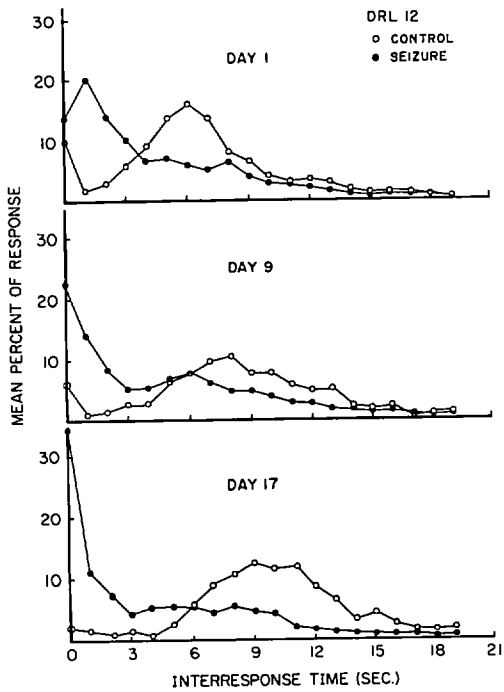


FIG. 1. Percentage distribution of interresponse times (IRTs) from sample sessions after the shift from a DRL-6-sec. to DRL-12-sec. schedule for rats that served as controls and rats in which limbic seizures had been elicited about two months previously by a single, systemic injection of lithium and pilocarpine

Visual inspection of IRT profiles clearly indicated that IRTs for the seizured rats were asymmetrically skewed within the shorter bins while those for the control rats were distributed normally around the schedule demands. For the DRL-6-sec. schedule, multivariate analysis of variance as a function of time block and group indicated statistically significant group ($F_{1,5} = 9.74$, $p < 0.05$; $F = 14.64$, $p < 0.01$, respectively) differences. The same two bin measures for the DRL-12-sec. schedule also indicated group ($F = 31.34$, 13.59) differences (Fig. 1). The absolute shifts in the interresponse times of the control rats were within the normal range for this laboratory.

Following collection of behavioral data, the brains were removed and fixed in ethanol-formalin-acetic acid (Persinger, *et al.*, 1988), and processed; coronal, 10-$\mu$m sections, obtained for every 200 $\mu$m of brain, were stained with toluidine blue O and examined (by the second author) over the entire area for necrosis. This was defined as conspicuous (at 100 x magnification) neuronal drop-out or gliosis.

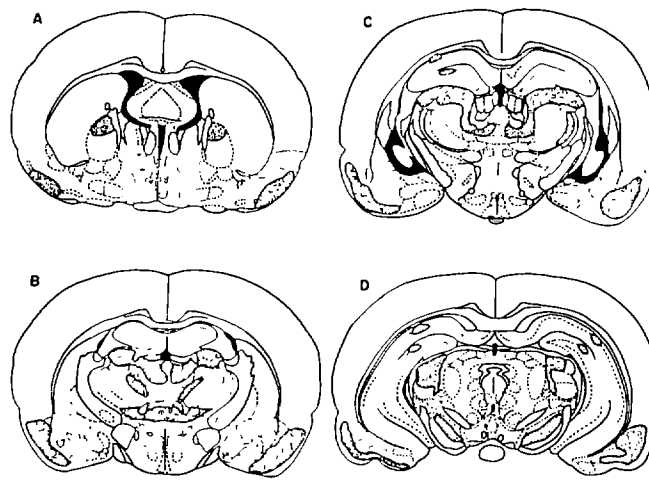


FIG. 2. Composite of damage within the brains of the four rats that had displayed limbic seizures as a consequence of systemic lithium-pilocarpine injections. Damage within the limbic cortex was manifested primarily as cystic lesions while damage within the thalamic and hippocampal regions was displayed as neuronal dropout and gliosis.

Commensurate with other studies (Persinger, *et al.*, 1988) extreme necrosis was noted in the amygdal, pyriform-entorhinal cortices (the latter being the major input to the hippocampus) and the dorsomedial and lateral posterior thalamic nuclear groups. These results indicate that despite the apparent behavioral recovery of these animals, as defined by casual observation, serious deficits in inhibitory capacity existed.

## REFERENCES

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